DETAILED ACTION

1. The remarks and amendments filed 15 March 2010 have been entered. Claims 1-10 and 12 are pending and under examination.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114 was filed in this application after a decision by the Board of Patent Appeals and Interferences, but before the filing of a Notice of Appeal to the Court of Appeals for the Federal Circuit or the commencement of a civil action. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 15 March 2010 has been entered.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 – 3 and 5 – 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim 2002 (Autonomic Neuroscience 102:8-12) in view of Donovan (U.S. Patent Application Publication 2001/0023243).

This rejection is maintained for the reasons previously made of record and upheld by the Board of Patent Appeals and Interferences. Briefly, Kim teaches sympathetically mediated

chronic pain is mediated by the sympathetic ganglion (see p. 8 first paragraph). While Kim did not treat human patients with sympathetic pain, the authors present the results of experiments indicating that botulinum toxin, when administered to the superior cervical ganglion, can inactivate the nerves in that ganglion and prevent them from having their effects. Type A toxin, recited in claims 1 – 2, was used by the authors in their experiments (see p. 9, section entitled "Surgical Procedure"). The dose used was 2 - 10 units per kilogram of body weight (p. 9, "Experimental animals"), administered to rabbits which is within the range recited in claim 3, given that rabbits weigh less than 30 kg. The reference teaches administration to the superior cervical ganglion as recited in claim 5 - 6. The data presented by Kim show that the toxin induces miosis, which is the constriction of the pupil within the eye. According to Kim, this indicates that botulinum toxin acts on the sympathetic neurons of the superior cervical ganglion (p. 11, second paragraph). Kim concludes that the histological findings were normal, indicating that botulinum toxin "may be used clinically as a safe neurolytic agent" (p. 11, paragraph spanning the two columns) and that the results indicate that the toxin is likely to be useful in treating sympathetically mediated pain, as recited in claim 1 (p. 11, final paragraph). However Kim does not teach administration to humans, and does not explicitly teach percutaneous injection as recited in claim 1. Rather Kim teaches administration rabbits and teaches direct administration to the ganglion following surgical opening of the skin and underlying tissues.

Donovan teaches that botulinum toxin A, recited in claims 1-2, can be administered to a human patient via percutaneous injection in order to achieve a block of nerves within the sympathetic ganglia. See for example paragraph [0090], which details that a percutaneous injection can be used, and paragraph [0092], which indicates that sympathetic ganglia can be targeted, that type A toxin should be used, and that human patients should be treated. Donovan also teaches that inactivating nerves within the celiac plexus is known to treat pain and that the methods known to block the celiac plexus can also be used to block sympathetic ganglia (paragraph [0090]). Donovan teaches that performing the methods of his invention, which include administration of botulinum toxin A to human patients by percutaneous injection to sympathetic ganglia, reduce pain (paragraph [0091]). Additionally, the teachings of Donovan indicate that the effects of botulinum toxin are not permanent, i.e. they are reversible as recited in independent claims 1 and 3. See for example paragraphs [0072], [0099], and [0110], which all indicate that the effects of botulinum toxin last for two to six months, and in certain circumstances up to 27 months. That the effect of the toxin ceases in as little as two months

indicates to one of ordinary skill in the art that the sympathetic block is reversible, as recited in claim 1. However, Donovan does not explicitly teach that the method is useful for treating sympathetically mediated chronic pain, as recited in claim 1.

It would have been obvious to one of ordinary skill in the art to modify the method of Kim, who teaches administration of botulinum toxin A to the superior cervical ganglion is sufficient to inactive nerves within that ganglion, by following the guidance of Donovan, who teaches that in order to inactivate nerves within a sympathetic ganglion one should administer botulinum toxin A to human patients via percutaneous injection, thereby arriving at the invention of claims 1 – 3 and 5 – 6. Kim suggests that botulinum toxin A will be useful as treatment for sympathetically mediated pain, and Donovan states that the same toxin is known to be effective in treating pain. This would necessarily be a reversible sympathetic block, as recited in claim 1. Note that the amendment to claim 1 merely recites an effect that is achieved by performing the method which is rendered obvious by the prior art teachings of Kim and Donovan.

At pp. 4-5 of the remarks filed 15 March 2010, applicant argues that the references cited by the examiner fail to render obvious the newly-added limitation. The examiner respectfully disagrees. First, it is important to note that the amendment ("... thereby achieving a reversible sympathetic block...") recites no additional starting materials or steps beyond those claims previously indicated by the examiner to be unpatentable under 35 USC 103(a). The amendment only characterizes the type of block which would be achieved once the method, which is itself obvious, is performed. Second, as explained above, the reference by Donovan provides indications that the effects of botulinum toxin are not permanent, but rather are reversible in that they wear off within as few as 2 months. One of ordinary skill in the art would have found the methods claimed obvious, and by performing these methods would have achieved a reversible block.

4. Claims 1 – 3 and 5 – 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim in view of Donovan as applied to claims 1 – 3 and 5 – 6 above, and further in view of Erickson 1993 (Radiology 188:707-709).

The reasons why claims 1 – 3 and 5 – 6 are obvious over Kim in view of Donovan are set forth above. However, neither of these references teaches administering a local anesthetic as a sympathetic block and identifying chronic pain as being mediated by the sympathetic nervous system as recited in claim 7.

Erickson teaches methods of administering local anesthetics, including lidocaine, bupivarcaine, and buprenophrine as sympathetic blocks. The specific drugs are listed in the abstract, and the first paragraph of the Materials and Methods section teaches that the stellate ganglion, which is a sympathetic ganglion, was the target. Erickson teaches the method is successful in human patients, as recited in claim 1, and leads to pain relief, including complete pain relief which is more than 50% of the perceived pain as recited in claim 7 (see results section). Erickson teaches that the duration of relief is generally short, between one hour and three weeks. However Erickson does not teach administration of botulinum toxin as recited in claim 1.

It would have been obvious to one of ordinary skill in the art to include the step of administering a short-acting local anesthetic as a sympathetic block, as taught by Erickson, when performing the methods of claims 1 – 3 and 5 – 6, which are rendered obvious by Kim and Donovan, thereby arriving at the invention of claim 7. The motivation to do so would be to ensure that the pain experienced by the patient is in fact mediated by the sympathetic ganglia. Performing this step would be advantageous, as it would ensure that those patients whose pain is not mediated by sympathetic ganglia will not be exposed to the toxin. Thus by performing the step taught by Erickson and recited in claim 7, the artisan would ensure identification of the patients most amenable to treatment.

Applicant did not traverse this rejection for reasons other than those discussed above. Accordingly, this rejection is maintained.

5. Claims 1 – 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim in view of Donovan as applied to claims 1 – 3 and 5 – 6 above, and further in view of Brushey (U.S. Patent Application Publication 2001/0056275).

The reasons why claims 1 – 3 and 5 – 6 are obvious over Kim in view of Donovan are set forth above. However, neither of these references teaches administration to a sympathetic ganglion and achieving a block of the splanchnic nerve when pain is in the lower extremities, as recited in claim 4.

Brushey discusses administration of anesthetics in order to decrease pain and teaches that when sympathetic pain is present in the lower extremities, the splanchnic nerve should be blocked (see paragraphs 0004 - 0005). However Brushey does not teach administration of botulinum toxin as recited in claim 1.

It would have been obvious to one of ordinary skill in the art to modify the methods rendered obvious by Kim and Donovan such that when the pain is present in the lower extremities, the toxin would be given to block the splanchnic nerve. The motivation to do so would be to effectively block pain, as Brushey teaches this is the nerve to be blocked when pain is present in the lower extremity, thereby guiding the artisan of ordinary skill to select this particular anatomic locus for treating this particular type of pain. As set forth above, this would necessarily be a reversible block, as Donovan teaches the effects of botulinum toxin wear off in as little as two months.

Applicant did not traverse this rejection for reasons other than those discussed above. Accordingly, this rejection is maintained.

6. Claims 1 – 3, 5 – 6, 8 – 10, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henrard 1982 (Arch Mal Coeur 75(11):1317-1320) in view of Kim and Donovan.

Henrard teaches treatment of coronary vasospasm which is on point to claims 8 – 9. This is a form of peripheral vascular disease, which is recited in both claims 8 – 9. Note that vasospasms are defined by applicant to be vascular diseases suitable for treatment with the invention (specification, p. 12 paragraph [61]). Henrard teaches that the spasms can be treated by homolateral thoracic sympathectomy, i.e. surgical removal of a sympathetic ganglion (see abstract translation on p. 1320). However Henrard does not teach administration of boutlinum toxin.

The reasons why claims 1 – 3 and 5 – 6 are obvious over Kim in view of Donovan are set forth above in section I and for the sake of brevity are not reiterated here. Note that the references provide guidance to select botulinum toxin A, the specific doses recited in the claims, human patients, and relief from pain as detailed above. Kim teaches pain relief by administering botulinum toxin to a sympathetic ganglion, which is on point to claims 8 and 10, and the doses as recited in claim 12. However, Kim does not teach administering botulinum toxin to patients with cardiovascular conditions as recited in claims 8 – 9.

Donovan teaches administration of botulinum toxin to sympathetic ganglia by percutaneous injection, and indicates that the effects of botulinum toxin wear off within 2 months, which is on point to the newly-added limitation in claims 8-9 ("... thereby achieving a

reversible sympathetic block...") but does not explicitly teach using this method to treat patients with the diseases recited in claims 8 – 9.

It would have been obvious to one of ordinary skill in the art to modify the method of Henrard by administering botulinum toxin to the sympathetic ganglion instead of removing the sympathetic ganglion, thereby arriving at the invention of claims 8 – 10 and 12. Henrard teaches that inactivating the ganglion by removal is sufficient for treatment of spasm, and using botulinum toxin for inactivation, as taught by Kim, would be advantageous as it would be less invasive. Additionally, selection of the method of administration taught by Donovan, namely percutaneous injection, would be advantageous as it would allow for the toxin to penetrate and inactivate the ganglia without requiring surgery. Note claim 10 is included in this rejection as it does not recite any additional starting materials or steps, but rather recites effects which will happen upon administration.

Applicant did not traverse this rejection for reasons other than those discussed above. Accordingly, this rejection is maintained.

Conclusion

7. No claim is allowed.

8. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. The examiner notes that the issues presented by these claims are the same as those decided by the Board of Patent Appeals and Interferences in the decision dated 26 January 2010 (*Ex parte* Ian Carrol, David Clark, and Sean Mackey, Appeal No. 2009-009980).

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
April 19, 2010